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Mini Review

Immune Tolerance in Liver

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Introduction

Immune tolerance, or immunotolerance, exhibits a bias toward immune unresponsiveness, both in the context of liver transplant and liver diseases. The concept of liver immune tolerance is original from early research in orthotopic liver transplantation. Liver transplanted between unrelated pigs were generally tolerated; whereas other organs transplanted were rejected unless treated with a powerful immunosuppressive drug. These results suggested the liver transplanted was imposing systemic immune tolerance. The liver is composed of a large reservoir of immune cells, these include neutrophils, dendritic cells, monocytes, resident macrophages (Kupffer cells), natural killer T cells, natural killer cells and liver resident lymphocytes (B, CD8+ T, CD4+ T cells), but liver tends to be immune unresponsive to transplantation, infection and liver cancer. The underlying mechanism of liver immunotolerance, however, remains unclear. In this review, we discuss emerging evidences to understand liver immunotolerance in the context of liver transplantation and diseases.

First of all, incompletely activation or entirely exhaustion of local T cells could result in liver tolerance. T cells are one of the important types of white blood cells in the immune system and play a critical role in the adaptive immune response. The function of T cells is immune mediated cell death. These are two subtypes of T cells: CD8+ and CD4+ T cells. The former acts as killer T cells, they are cytotoxic, which means that they can directly kill virus infected cells, as well as cancer cells. The latter CD4+ T cells function as "help cells", they mainly help CD8+ T cell activation, which leads to a larger immune response. The liver regards as a secondary lymphoid organ, priming CD8+ T cells locally, rather than in draining lymph nodes. In mouse model, CD8+ T cells are rapidly activated locally in the liver; while the transplanted liver in a recipient that cannot activate CD8+ T cells. Subsequently, such incomplete activation might trigger T cell apoptosis, which leads to liver tolerance [1]. Moreover, many liver infections result in relatively poor CD4+ T-cell activation, which may be because liver antigen-presenting cells express a variety of inhibitory cytokines and co-inhibitory ligands. In the setting of liver transplants, local T-cell activation promotes liver tolerance. In addition, mice suffered with chronic lymphocytic choriomeningitis virus fail to eliminate the virus, which is associated with exhausted T cells. These exhausted T cells exhibit a characteristic phenotype, including the markers programmed cell death 1 (PD-1), lymphocyte activation gene 3 (Lag-3) and Cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Once T cells express those markers, they would sequentially lose their cytotoxic function. Eventually, these exhausted T cells could not effectively kill the virus or cancer cells in the liver [2].

Secondly, Macrophage's act as agents mediated liver tolerance. There is a population of resident macrophages in the liver sinusoids, Kupffer cells (KC), which show multiple immunosuppressive activity and impose the liver immune unresponsiveness. Liver plays a critical role in inducing tolerance to pathogenic invaders during infection. Based on previous research, there are at least two mechanism are involved in KC mediated tolerance. On the one hand, KC express large amount of Fast ligand and will kill CD8+ T cells that could recognize them. On the other hand, KC also express other surface molecules that participate in liver tolerance [3]. For example, B7H1, also named PD-L1, a ligand that engages PD-1 receptor on T cells, leading to T cell exhaustion [4]. Intriguingly, researchers take advantage of this phenomenon and attempt to

rescue exhausted T cells. They discover specific antibody to block PD-1/PD-L1 interaction and recover T cell activity, which shows very promising clinical results in liver cancer patients. Additionally, the deep mechanistically study from Xu et al showed that Kupffer Cells in HBV carrier mice expressed more IL-10 and mediated the systemic tolerance induction in an IL-10 dependent manner [5].

Aside from Kupffer cells, dendritic cells and liver sinusoidal endothelial cells (LSECs) contribute to liver tolerance as well. Dendritic cells are a diverse population of cells specialized for antigen presentation. There is an evidence that dendritic cells tend to induce tolerance. In a mouse model, liver dendritic cells highly express PD-L1, which in turn suppress liver allograft rejection [6]. Tolerance-inducing liver dendritic cells are synchronized with other cell types. For example, liver dendritic cells promote Treg cells development and generate an immunosuppressive product, like kynurenine [7]. Additionally, LSECs can be efficient antigen presenting cells in the liver. They can take up antigen and present it to T cells. However, the outcome of antigen-presentation by LSECs causes CD8+ T cell tolerance rather than immunity. Diehl et al reports LSEC could initially stimulate naïve T cells but fail to support differentiation into effector cells, and induce T cell tolerance [8].

In conclusion, liver contains a complex immune microenvironment. As mentioned above, liver immune tolerance is maintained by dendritic cells, liver sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and hepatocytes. The presentation of antigens to T cells by various cell types results in abortive activation tolerance, exhaustion, or apoptosis. Liver tolerance might favor liver transplantation as the tolerant environment is benefit for donor liver. Nonetheless, acceleration cancer cells growth or virus infection leads to diseases progression in the setting of liver immune tolerance. One possibility of many malignant tumours such as colon carcinoma or melanoma metastasize into the liver is due to liver immune unresponsiveness and tumor cells evade immune surveillance. Recently, abolishment of liver tolerance and boost liver immunity is a popular research direction for people who focus on liver cancer therapy. Even though the past research advanced our understanding of liver immunotolerance, we still need to pay more attention the mechanistical research and develop more potential therapeutical approaches, as it plays a crucial role in liver disease.

Acknowledgment

None.

Conflict of Interest

None.

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